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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,242	06/02/2000	James McKim	28341/6281A	6518

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EXAMINER	
WITZ, JEAN C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,242	MCKIM ET AL.	
	Examiner	Art Unit	
	Jean C. Witz	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-19 and 21-38* is/are pending in the application.

4a) Of the above claim(s) *12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4,5, 7-11, 21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to the rejections of record have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 4-5, 7-11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fricker combined with General & Applied Toxicology, pages 11-20 in view of Eisenbrandt et al. and Renwick et al., and further in view of Yao et al., Chung et al., Garza-Ocanas et al., and Morrison et al.

The claims recite a method of predicting the in vivo toxicity of a chemical compound which involves culturing cells at four or more concentrations of the chemical compound and measuring three indicators of cell health in those four or more concentrations of the chemical and predicting a toxic concentration of the chemical by performing dose response analyses of the results of the test measurements and selecting a toxic concentration which is less than or equal to the highest measurement of the chemical producing no observable effect in any of the indicators of cell health tested.

Fricker discusses the role of in vitro cytotoxicity testing in the selection and development of pharmaceuticals. In the introduction, the reference states that potential new products must be first assessed for performance but toxicity becomes important where such toxicity may place limitations on the products usefulness. The reference teaches that cytoxicity testing is an effective way of further ranking the potential products and provides a simple method for selecting candidates for further investigation. The paper concludes that cytotoxicity testing can be used to rank similar chemicals or materials where a knowledge of relative toxicity is required and as such can be incorporated into the selection procedure of a product research and development program.

General & Applied Toxicology, pages 11-20, discusses the importance of dose response analyses in toxicology testing. By plotting dose response curves, the slope of the curve can provide important information about toxicity of the chemical tested and assist in selection of doses that will be both therapeutic and relatively non-toxic. On page 15, the reference states that when dealing with drugs, comparison of a pharmacological response curve with a dose response curve for mortality to determine a therapeutic index is a simplistic method for assessing safety. The reference states that a complete appraisal of safety-in-use includes other considerations. Finally, at page 16, the reference states that for many toxic effects, there is a dose below which no effect or response can be elicited. This dosage is considered the threshold dosage and dosages below this level can be used to determine a "no observable effect level"

(NOEL) that can be used as a basis for assigning safe levels for exposure to the chemical.

Use of the NOEL dose is conventional in the art of toxicology evaluations per the teaching of Eisenbrandt et al. and Renwick et al. Eisenbrandt et al, when addressing the neurotoxic potential of chemicals, teaches that an assessment of potential toxicity should be based upon a number of different parameters that are derived from a variety of toxicological tests at relevant dose levels. A combination of functional and morphological tests enhances the ability to discover toxicity. Specialized tests should be performed at dose levels where no adverse general effects were detected with routine toxicity studies because substance with toxic effects at levels that are less than the NOEL level for other toxic effects would be of concern. Therefore, Eisenbrandt et al. clearly suggests that multiple tests that address different effects are critical to determinations of toxicity of a substance.

Renwick et al. shows that the NOEL dosage is conventionally chosen as a "safety" level for determination of acceptable daily intake of chemicals such as food additives and environmental chemicals.

Finally, the disclosure of Yao et al., Chung et al., Garza-Ocanas et al., and Morrison et al. was discussed in the previous office action. These references, taken as a whole, show that it is conventional to use multiple tests, and specifically the elected specie tests, to evaluate the cytotoxicity of a test compound. It is also conventional to use multiple concentrations within those claimed. The use of controls is also shown to be conventional. Creating graphs of data is also deemed conventional.

It would have been obvious to one of ordinary skill in the art at the time the invention was made, in order to predict the in vivo cytotoxicity of a chemical, to select at least three conventional cytotoxicity tests, to use multiple concentrations, to use a control and to graph the results. The claims recite the selection of two values: the Ctox and the Cther, and the calculation of the ETI. The prior art documents taken as a whole indicate that the selection of a safety dose is within the skill of the practitioner where one would be motivated to select the NOEL dose in order to be more assured that fewer toxic effects would result from administration of the NOEL dose. General & Applied Toxicology teaches that comparison of toxicological dose response curves and therapeutic dose response curves is conventional and that the calculation of a therapeutic index based upon a ratio of these curves. It is deemed prima facie obvious to one of ordinary skill in the art at the time the invention was made that chemicals that show greater therapeutic effect while at the same time showing lower toxicity would be preferred for further development. It would be illogical to select a chemical that showed similar therapeutic effect but higher toxicity.

Finally, all of the other methods are permutations of conventional uses of standard cyotoxicity tests. Toxicity tests are conventionally performed when one of ordinary skill in the art is developing an agent for treatment of a disease or disorder, is identifying a lead compound for drug development, is screening chemical compounds to select candidate therapeutic agents, is prioritizing candidate therapeutic agents for

pharmaceutical research and is predicting in vivo toxicity of chemical compounds. In fact, FDA regulations require the submission of toxicity tests for evaluation when one of ordinary skill in the art is submitting a new drug application to the agency for approval.

Therefore, if it would have been obvious to use the toxicity evaluation method such as claimed, it would have been similarly prima facie obvious to engage in the other methods as claimed.

The full text of the references cited in the previous office action have been included for Applicants' convenience.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (571) 272-0927. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jean C. Witz
Primary Examiner
Art Unit 1651